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EP 0 251 459 B1

Description

The present invention relates to a solid controlled release pharmaceutical composition.

A "controlled releas pharmaceutical composition" is one that achieves slow release of a drug over an extended period of time and extends the duration of drug action over that achieved by conventional delivery. Preferably such a composition maintains drug level in the blood or target tissue within the therapeutic range for 8 hours or more.

A controlled (sustained) release pharmaceutical composition containing an active ingredient has many advantages over a normal release form of the same ingredient. These include a reduction of the frequency of administration, a decrease in side effects and the maintenance of effective concentrations of the active material in the blood.

Pharmaceutical compositions comprising an active ingredient incorporated in a matrix comprising beta-cyclodextrin and inter alia polyethylene glycol are known from FR-A-2496460.

Controlled release compositions comprising an active ingredient and a complex between a cellulose polymer and a C_{8-18} aliphatic alcohol are described in EP-A-0032004. US-A-3965256 describes slow release compositions comprising a combination of a higher aliphatic alcohol and a hydrated hydroxy-alkyl cellulose in ratio of from 2:1 to 4:1 parts by weight.

It is an object of the present invention to provide a controlled release pharmaceutical composition that xercises particularly good control over the release of the active ingredient.

Other objects and advantages of the present invention will become apparent from the following detailed d scription thereof.

According to the present invention, therefore, there is provided a solid, controlled release, pharmaceutical composition comprising an active ingredient incorporated in a matrix comprising a first substance selected from a water-soluble polydextrose and a water-soluble cyclodextrin and a second substance selected from a C_{12}-C_{36} fatty alcohol.

In the present specification, "water soluble" means that the polydextrose or cyclodextrin dissolves to a level of at least 1% (w/w) in water at 25 °C.

Although the polydextrose employed in the present composition may have an average molecular weight of between about 360 and 10^6, preferably the polydextrose has a number average molecular weight between 1000 and 12000. Polydextrose is a non-nutritive polysaccharide, prepared by the condensation polymerisation of saccharides in the presence of polycarboxylic acid catalysts, under reduced pressure.

Polydextrose is described in US Patents No. 3766105 and 3786794 (the contents of which documents are incorporated herein by reference) and is available from Pfizer Inc., New York. Commercially available polydextrose polymer is generally a low molecular weight, water-soluble, randomly bonded polymer of glucose containing minor amounts of sorbitol end groups and citric acid residues attached to the polymer by mono- and di-ester bonds. The number average molecular weight of this commercially available material is 1500, ranging from about 360 to about 20,000.

In the present specification, "cyclodextrin" incorporates both the naturally occurring clathrates obtained from the action of Bacillus macerans amylase on starch to form homogeneous cyclic alpha (1-4) linked D-glucopyranose units (ie. alpha, beta- and gamma-cyclodextrin) but also the methylated derivatives of these natural products, especially of beta-cyclodextrin (eg. heptakis (2,6-di-0-methyl)-beta-cyclodextrin and heptakis (2,3,6-tri-0-methyl)-beta-cyclodextrin.

In a preferred embodiment of the present composition the cyclodextrin (or methylated derivative) is a beta-cyclodextrin.

The amount of polydextrose and/or cyclodextrin present in the composition of this invention will be determined by a number of factors, including the active ingredient to be administered and the rate of drug release required. Preferably, however, the composition will contain between 1% and 80% (w/w), especially between 1% and 50% (w/w) of polydextrose and/or cyclodextrin, most especially between 2% and 40% (w/w) of polydextrose and/or cyclodextrin.

The C_{12}-C_{36} fatty alcohol may be any digestible, long chain alcohol. Preferably, it has a melting point between 25° and 95 °C. In a particularly preferred embodiment of this invention, the alcohol is a C_{14}-C_{22} fatty alcohol such as stearyl alcohol, myristyl alcohol, cetyl alcohol and, which is preferred, cetostearyl alcohol.

In addition to the polydextrose, cyclodextrin and alcohol, the present composition may also include further ingredients which can contribute to th control of the active ingredient's release and are compatible with polydextrose, cyclodextrin and fatty alcohol.

Of these polymers, the cellulose ethers, especially hydroxyalkylcelluloses and carboxyalkylcelluloses, most especially hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose and sodium

carboxymethyl cellulose, are preferr d.

In preferred compositions according to this invention the ratio of polydextrose/cyclodextrin/hydrophilic and/or hydrophobic polymer to fatty alcohol is between 6 to 1 and 1 to 6, especially between 4 to 1 and 1 to 4.

When the polydextrose and/or cyclodextrin is combined with the C_{12}-C_{36} fatty alcohol the matrix itself is novel. Thus, in another aspect of the present invention, there is provided a preparation for use in the production of a solid, controlled release pharmaceutical composition comprising a matrix of a first substance selected from a water-soluble polydextrose and a water-soluble cyclodextrin and a second substance selected from a C_{12}-C_{36}, especially C_{14}-C_{22}, fatty alcohol. Optionally the matrix may also contain at least one of a hydroxyalkyl cellulose and a carboxyalkyl cellulose. Preferably the ratio of polydextrose/cyclodextrin/ cellulose to fatty alcohol is between 6 to 1 and 1 to 6, especially between 4 to 1 and 1 to 4.

In addition to the above materials, the present controlled release composition may also contain excipients, such as binders, disintegrating agents, colours, flavours, preservatives, stabilisers, glidants and lubricants, the use of which will be well known to those skilled in the pharmaceutical art.

Although the present controlled release composition may be in any solid dosage form, for example, a suppository or a pessary, it is preferably adapted for oral administration. In the present specification "oral administration" incorporates buccal and sublingual administration. Thus, the preferred oral dosage forms include tablets, buccal tablets, sublingual tablets, lozenges, capsules containing, for example, granules or pellets, and dragees.

Any active ingredient that may be administered by the oral, buccal, sublingual, rectal or vaginal routes may be employed in the controlled release composition of this invention. Those medicaments having a biological half-life below about 8 hours, however, are particularly suitable for incorporation in the present composition.

Examples of active ingredients that may advantageously be incorporated in the present composition are,

1) Anti-allergic drugs, such as cyclizine, dimethindene maleate and triprolidine hydrochloride,
2) Anti-diabetic drugs, such as chlorpropamide, glibenclamide, metformin and tolbutamide,
3) Hormones,
4) Antiarrhythmic agents, such as disopyramide, procainamide, propranolol and quinidine,
5) Anti-inflammatory agents, such as aspirin, diclofenac sodium flurbiprofen, ibuprofen, indomethacin, ketoprofen, naproxen and phenylbutazone,
6) Antiemetic drugs, such as metoclopramide,
7) Diuretics, such as amiloride, ben drofluazide, bumetanide, cyclopenthiazide, ethacrynic acid, frusemide, hydrochlorothiazide, triampterene, chlorthalidone and spironolactone,
8) Anti-anginal agents, such as nitrogylcerin, isosorbide dinitrate pentaerythritol tetranitrate, verapamil and diltiazem.
9) Vasodilators, such as nifedipine, naftidrofuryl oxalate, and nicardipine,
10) Antihypertensive agents, such as clonidine, indoramin, guanethidine, methyldopa, oxprenolol, captopril, hydralazine and propranolol,
11) Bronchodilators, such as salbutamol, isoprenaline and terbutaline,
12) CNS stimulants, such as caffeine and amphetamine,
13) Anti-histamines, such as clemastine fumarate, mepyramine, chlorpheniramine, brompheniramine, diphenhydramine.
14) Analgesic agents, such as morphine, codeine, phenazocine, dihydrocodeine, hydromorphone, meptazinol, phenacetin, pethidine, paracetamol, oxycodone, diamorphine, nalbuphine, buprenorphine, and mefenamic acid,
15) Vitamins, such as Vitamin B1, Vitamin B2, Vitamin B6, Vitamin C and Vitamin E,
16) Antidepressants, such as lofepramine, amitriptyline, doxepin, maprotiline, imipramine, desipramine and mianserin,
17) Tranquilisers, such as chlordiazepoxide and diazepam,
18) Hematinic agents, such as ferrous fumarate,
19) Respiratory stimulants, such as nikethamide,
20) Antibacterial agents, such as polymyxin, streptomycin, sulphonamides, penicillins, erythromycin, cephalosporins, nalidixic acid, tetracyclines, hexamine salts, gentamicin and nitrofurantoin,
21) Hypnotic agents such as barbiturates, dichloral phenazone, nitrazepam and temazepam,
22) Antiviral agents, such as idoxuridine,
23) Vasoconstrictors, such as angiotens in amide, dihydroergotamine, and ergotamine,

24) Topical anaesthetics, such as benzocaine,
25) Anticholinergic agents, such as scopolamine, atropine and propanthelin ,
26) Adrenergic drugs, such as phenylephrine hydrochloride, phenylpropanolamine hydrochloride and pseudoephedrine,
27) Anthelmintic agents, such as diethylcarbamazine,
28) Corticosteroids, such as dexamethasone, prednisone, prednisolone and triamcinolone acetonide,
29) Inorganic drugs, such as lithium carbonate, potassium chloride and lithium sulphate,
30) Antacids, such as aluminium trisilicate and aluminium hydroxide,
31) Antiulcer agents, such as cimetidine and ranitidine,
32) Cofactors, such as nicotinic acid,
33) Antipsychotic agents, such as thioridazine, trifluoperazine, fluphenazine and haloperidol,
34) Laxatives, such as bisacodyl and magnesium hydroxide,
35) Antiperistaltic agents, such as diphenoxylate,
36) Anticoagulant agents, such as warfarin,
37) Haemostatic agents, such as epsilon-aminocaproic acid,
38) Antinauseant agents, such as metoclopramide, pyridoxine and prochlorperazine,
39) Anticonvulsant agents, such as sodium valproate and phenytoin sodium,
40) Neuromuscular drugs, such as dantrolene sodium,
41) Hypoglycaemic agents, such as chlorpropramide, glucagon and tolbutamide,
42) Thyroid drugs, such as thyroxine, triiodothyronine and propylthiouracil,
43) Uterine relaxant, such as ritodrine,
44) Appetite suppressants, such as phentermine, diethylpropion HCl and fenfluramine HCl,
45) Erythropoietic substances, such as folic acid, calcium gluconate, and ferrous sulphate,
46) Expectorants, such as carbocisteine and, guiaphenesin,
47) Cough suppressants, such as noscapine, dextromethorphan and oxycodone,
48) Antiuricemic drugs, such as allopurinol, probenecid and sulphinpyrazone,

Preferably the active ingredient is a water-insoluble drug. In the present specification, a water insoluble drug is a drug that dissolves in water (pH 5) at 20°C to a concentration of less than 1.0mgml^{-1}, preferably l ss than 0.5mgml^{-1}.

According to another feature of the present invention, the solid, controlled release, pharmaceutical composition is prepared by mixing an active ingredient with a first substance selected from a water soluble polydextrose and a water soluble cyclodextrin and a second substance selected from a C_{12}-C_{36} fatty alcohol optionally in the presence of one or more of the following excipients, a hydrophilic or hydrophobic polymer, a binder, a disintegrating agent, a colour, a flavour, a preservative, a stabiliser, a glidant and a lubricant. Preferably the alcohol is a C_{14}-C_{22} fatty alcohol.

In a particularly preferred embodiment of this feature of the invention a solid, controlled release, pharmaceutical composition, in unit dosage form and for oral administration (as hereinbefore defined), is prepared by granulating an active ingredient with a first substance selected from a water soluble polydextrose and a water soluble cyclodextrin and, optionally, mixing with one or more of the following excipients, a hydrophilic or hydrophobic polymer (other than polydextrose), a binder, a disintegrating agent, a colour, a flavour, a preservative, a stabiliser, a glidant or a lubricant, to form granules, mixing the granules formed with a second substance selected from a C_{12}-C_{36} fatty alcohol and compressing the granules to give an oral, solid, unit dosage form containing a predetermined, therapeutically active, quantity of the active ingredient. Preferably the alcohol is a C_{14}-C_{22} fatty alcohol.

Depending on the particular case, the method of preparation of the granules may involve for example wet granulation or direct compression.

Once the oral, solid unit dosage form has been prepared it may, if desired, be coated, for example with a gastro-resistant coating.

In a further, particularly preferred embodiment of this feature of the invention a solid, controlled release, pharmaceutical composition in the form of a capsule is prepared by pelletising, spheronising or granulating an active ingredient with a first substance selected from a water soluble polydextrose and a water soluble cyclodextrin and a second substance selected from a C_{12}-C_{36}, especially C_{14}-C_{22}, fatty alcohol and, optionally, one or more of the optional ingredients employed in the preparation of th oral, unit dosage form above, to form pellets, spheroids or granules and encapsulating the pellets, spheroids or granules to give a capsule containing a predetermined, therapeutically active, quantity of the active ingredient.

Prior to filling the capsule with the pellets, the spheroids or the granules, the pellets/spheroids/granules may be coated, for example with a gastro-resistant coating.

According to another feature of the present invention, there is provided a process for the preparation of

a matrix for admixture with an active ingredient to form a controlled release pharmaceutical composition comprising mixing a first substanc selected from a water soluble polydextrose and a water soluble cyclodextrin with a second substance selected from a C_{12}-C_{36} especially a C_{14}-C_{22}, fatty alcohol to form a controlled releas matrix

Once the matrix has been granulated it can then be mixed with a predetermined amount of the active ingredient and, optionally compressed, to give a controlled release pharmaceutical composition according to the invention.

Predetermined release patterns of unusually reliable and constant characteristics can be secured using the present composition. This is often very important medically, especially when treating patients having coronary diseases, such as angina pectoris, or related problems, such as circulatory disorders or abnormal blood pressure, or when treating psychotropic disorders, such as manic depression or schizophrenia or when treating bronchial disorders or moderate to severe pain. The present composition may also be extremely useful in the treatment of ulcerated tissues or mucous lesions and other conditions which arise from local hyperacidity or metabolic dysfunction in the physiological system. The present composition is therefore extremely versatile and adaptable giving a wide range of application and end use.

The present solid, controlled release, pharmaceutical composition, together with methods for its preparation will now be described by way of example only, with particular reference to the Figures in which,

Figure 1 compares the release rates of two pyridoxine hydrochloride controlled release formulations, one containing hydroxyethylcellulose and cetostearyl alcohol, the other polydextrose and cetostearyl alcohol, and

Figure 2 compares the release rates of two metoclopramide hydrochloride controlled release formulations, one containing hydroxyethylcellulose and cetostearyl alcohol, the other polydextrose and cetostearyl alcohol.

Example 1 (Comparative)

Pyridoxine hydrochloride (10gm) and hydrogenated castor oil (1.5gm) were granulated with hydroxyethylcellulose (2.0gm, Natrosol 250HX) and the granules were sieved through a 16 mesh screen and dried in a FBD at 60°C.

To the pyridoxine hydrochloride containing granules, molten cetostearyl alcohol (3.5gm) was added. This mixture was allowed to air cool and then passed through a 16 mesh screen.

Talc (0.3gm) and magnesium stearate (0.1gm) were mixed with the granules. This mixture was compressed to give 100 tablets each containing,

	mg/tablet
Pyridoxine HCl	100
Hydroxyethylcellulose	20
Hydrogenated castor oil	15
Cetostearyl alcohol	35
Talc	3
Magnesium stearate	1

Example 2

The procedure of Example 2 was followed except that polydextrose replaced the hydroxyethylcellulose. This gave 100 tablets each containing,

	mg/tablet
Pyridoxine HCl	100
Polydextros	20
Hydrogenated castor oil	15
Cetostearyl alcohol	35
Talc	3
Magnesium stearate	1

A comparison of the release rates of pyridoxine HCl from tablets prepared as described in Examples 1 and 2 is shown in Figure 1. The dissolution rates were measured by the USP Paddle Method at 100 rpm in 900 ml of aqueous buffer (pH 6.5).

Example 3 (Comparative)

Metoclopramide HCl (3gm) was wet granulated with anhydrous lactose (17gm) and hydroxyethylcellulose (2gm; Natrosol 250HX) and the granules were sieved through a 16 mesh screen. The granules were then dried in an FBD at 60°C.

To the warmed metoclopramide containing granules was added molten cetostearyl alcohol (7gm). The mixture was allowed to air cool and then passed through a 16 mesh screen.

Talc (0.6gm) and magnesium stearate (0.4gm) were mixed with the granules. The granules were then compressed to give 100 tablets each containing,

	mg/tablet
Metoclopramide HCl	30
Anhydrous lactose	170
Hydroxyethylcellulose	20
Cetostearyl alcohol	70
Talc	6
Magnesium stearate	4

Example 4

Anhydrous lactose (17gm) and polydextrose (2gm) were dry mixed. Molten cetostearyl alcohol (7gm) was added to the dry mixed powders. The mixture was allowed to cool and then passed through a 16 mesh screen.

Metoclopramide HCl (3gm), talc (6gm) and magnesium stearate (4gm) were then mixed with the polydextrose/wax granules and compressed to give 100 tablets each containing,

	mg/tablet
Metoclopramide HCl	30
Anhydrous lactose	170
Polydextrose	20
Cetostearyl alcohol	70
Talc	6
Magnesium stearate	4

A comparison of the release rates of metoclopramide HCl from tablets prepared as described in Examples 3 and 4 is shown in Figure 2. The dissolution rates were measured by the USP Paddle Method at 100 rpm in 900 ml of aqueous buffer (pH 6.5).

Example 5

A complex of indomethacin and beta-cyclodextrin was prepared as described in GB 2016499A,

Example 1.

The indomethacin complex (360gm), lactose (20gm) and dicalcium phosphate (62mg) were wet granulated and the granules were sieved through a 16 mesh screen. The granules were then dried in a FBD at 60 ° C.

To the warned indomethacin containing granules was added molten cetostearyl alcohol (80gm). This mixture was allowed to air cool and then passed through a 16 mesh screen. Talc (2.0gm) and magnesium stearate (1.0gm) were then mixed with the granules. The granules were then compressed to give 100 tablets each containing;

	mg/tablet
Indomethacin complex	360.0 (equivalent to 50mg indomethacin)
Lactose, anhydrous	20.0
Dicalcium phosphate	62.0
Cetostearyl alcohol	80.0
Talc	2.0
Magnesium stearate	1.0

Examples 6-7

Examples 2 and 4 were repeated except that heptakis (2,6-di-0-methyl)-beta-cyclodextrin replaced polydextrose.

Example 8

Polydextrose (12.6gm) was mixed with molten cetostearyl alcohol (5.4gm). The granules were allowed to cool and sieved through a 20 mesh screen.

Metoclopramide HCl (3.0gm) was dry mixed with the polydextrose/alcohol granules and purified talc (0.21gm). Prior to compression, magnesium stearate (0.21gm) and purified talc (0.21gm) were mixed with the granules. This mixture was then compressed to give 100 tablets each containing.

	mg/Tablet
Metoclopramide	30
Polydextrose	126
Cetostearyl Alcohol	54
Purified Talc	4.2
Magnesium Stearate	2.1

Example 9

The procedure of Example 8 was followed except that the amounts used were chosen such that each tablet contained,

	mg/Tablet
Metoclopramide HCl	30
Polydextrose	210
Cetostearyl Alcohol	90
Purified Talc	6.6
Magnesium Stearate	3.3

Example 10

The procedure of Example 8 was followed except that the amounts used were chosen such that each tablet contained,

	mg/tablet
Metoclopramide HCl	30
Polydextrose	420
Cetostearyl Alcohol	180
Purified Talc	12.6
Magnesium Stearate	6.3

Example 11

Salbutamol sulphate (0.964gm), equivalent to 0.8gm base salbutamol was wet granulated with anhydrous lactose (20.8gm), polydextrose (1.25gm) and povidone (0.3gm) and the granules were sieved through a 16 mesh screen. The granules were then dried in a FBD at 60°C.

To the warmed salbutamol containing granules was added molten cetostearyl alcohol (5.5gm). The mixture was allowed to air cool and then passed through a 16 mesh screen.

Talc (0.8gm) and magnesium stearate (0.4gm) were mixted with the granules. The granules were then compressed to give 100 tablets each containing,

	mg/Tablet
Salbutamol Sulphate	9.64
Lactose, anhydrous	208
Polydextrose	12.5
Povidone (K30)	3
Cetostearyl Alcohol	55
Talc	8
Magnesium Stearate	4

The in-vitro dissolution rate of these tablets was measured by the USP Paddle Method at 100rpm in 900ml of aqueous buffer (pH 6.5). Results are given in Table 3.

Table 3

In vitro Dissolution of Salbutamol Tablets	
Time (Hours)	% (by wt) Released
1	49.5
2	62.4
3	73.2
4	79.1
5	85.5
6	91.0

Example 12

Th procedure of Example 11 was followed except that the amounts us d were chosen such that each tablet contained,

	mg/tablet
Salbutamol Sulphate	9.64
Lactose, anhydrous	190.36
Polydextrose	30
Povidone (K30)	3
Cetostearyl Alcohol	55
Talc	8
Magnesium Stearate	4

The in-vitro dissolution rate of the tablets was measured as described in Example 11. Results are given in Table 4.

Table 4

In Vitro Dissolution of Salbutamol Tablets	
Time (Hours)	% (by wt) Released
1	43.8
2	61.1
3	71.4
4	77.9
5	80.9
6	82.3

Example 13

The procedure of Example 12 was followed except that the amounts used were chosen such that each tablet contained,

	mg/tablet
Salbutamol Sulphate	9.64
Lactose, anhydrous	160.36
Polydextrose	60
Povidone	3
Cetostearyl Alcohol	55
Talc	8
Magnesium Stearate	4

Results are given in Table 5.

Table 5

In Vitro Dissolution of Salbutamol Tablets	
Time (Hours)	% (by wt) Released
1	41.0
2	57.8
3	68.0
4	74.6
5	81.0
6	83.1

Example 14

Quinidine polygalacturonate (41.25gm), lactose (4.5gm), hydroxypropylmethyl cellulose (1.25gm) and polydextrose (4.5gm) were granulated with water. The granules were sieved through a 16 mesh screen and dried in a fluid bed dried. The granules were mixed with molten cetostearyl alcohol (9.0gm) and allowed to cool. The granules were sieved through a 16 mesh screen and blended with purified talc (1.0gm). The granules were sieved through a 16 mesh screen and dried in a fluid bed drier. The granules were compressed to give 100 tablets each containing,

	mg/tablet
Quinidine Polygalacturonate	412.5
Lactose	45
Hydroxypropylmethyl cellulose	12.5
Polydextrose	45
Cetostearyl Alcohol	90
Purified Talc	10

The in-vitro dissolution rate of these tablets was measured by the USP Paddle Method at 100rpm in 900ml of buffer (pH 6.5).

The in-vitroo dissolution rate of these tablet was measured by the USP Paddle Method at 100rpm in 900ml of buffer (pH 6.5). Results are given in Table 6.

TABLE 6

In Vitro Dissolution of Quinidine Tablets	
Time (Hours)	% (by wt) Released
1	15.2
2	26.0
4	41.5
8	60.1
12	72.5
16	79.9
20	89.9

Claims

1. A solid, controlled release, pharmaceutical composition comprising an active ingredient incorporated in a matrix comprising a first substanc selected from a water soluble polydextrose and a water soluble cyclodextrin and a second substance selected from a C_{12}-C_{36} preferably a C_{14}-C_{22} fatty alcohol.

2. A composition according to claim 1 characterised in that the first substance comprises a cyclodextrin, preferably a beta-cyclodextrin.

3. A composition according to either claim 1 or claim 2 characterised in that the second substance comprises a C_{14}-C_{22} fatty alcohol, preferably stearyl alcohol, myristyl alcohol, cetyl alcohol or cetostearyl alcohol.

4. A composition according to any of claims 1 to 3 characterised in that it additionally contains a cellulose ether, preferably a hydroxyalkylcellulose or a carboxyalkyl cellulose.

5. A composition according to any one of claims 1 to 4 characterised in that the ratio of polydextrose/cyclodextrin/cellulose ether to fatty alcohol in the composition is between 6 to 1 and 1 to 6, preferably between 4 to 1 and 1 to 4.

6. A composition according to any one of claims 1 to 5 characterised in that the composition contains between 1% and 80% (w/w), especially between 1% and 50% (w/w), of the first substance.

7. A composition according to claim 6 characterised in that the composition contains between 2% and 40% (w/w) at the first substance.

8. A composition according to any one of claims 1 to 7 characterised in that the active ingredient comprises a water insoluble drug.

9. A preparation for use in the production of a solid, controlled release pharmaceutical composition comprising a matrix of a first substance selected from a water soluble polydextrose and a water soluble cyclodextrin and a second substance selected from a C_{12}-C_{36}, preferably a C_{14}-C_{22}, fatty alcohol.

10. A preparation according to claim 9 characterised in that the first substance comprises a cyclodextrin, preferably a beta-cyclodextrin, and the second substance comprises a C_{14}-C_{22} fatty alcohol, preferably stearyl alcohol, myristyl alcohol, cetyl alcohol or cetostearyl alcohol.

Revendications

1. Une composition pharmaceutique solide à libération contrôlée comprenant un ingrédient actif incorporé dans une matrice comprenant une première substance choisie parmi un polydextrose soluble dans l'eau et un cyclodextrine soluble dans l'eau et une deuxième substance choisie parmi un alcool gras en C_{12} - C_{36}, de préférence en C_{14} - C_{22}.

2. Une composition suivant la revendication 1, caractérisée en ce que la première substance comprend un cyclodextrine, de préférence un beta-cyclodextrine.

3. Une composition suivant la revendication 1 ou la revendication 2, caractérisée en ce que la deuxième substance comprend un alcool gras en C_{14} - C_{22}, de préférence l'alcool stéarylique, l'alcool myristilique, l'alcool cétylique ou l'alcool cétostéarylique.

4. Une composition suivant l'une quelconque des revendications 1 à 3, caractérisée en ce que elle contient en plus un éther cellulosique, de préférence une hydroxyalkylcellulose ou une carboxyalkylcellulose.

5. Une composition suivant l'une quelconque des revendications 1 à 4, caractérisée en ce que le rapport de polydextrose/cyclodextrine/éther cellulosique sur l'alcool gras dans la composition est compris entre 6 sur 1 et 1 sur 6, de préférence entre 4 sur 1 et 1 sur 4.

6. Une composition suivant l'une quelconqu des revendications 1 à 5, caractérisée en ce que la composition contient entre 1% et 80% (p/p), spécialement entre 1% et 50% (p/p), de la première substance.

7. Une composition suivant la revendication 6, caractérisée en ce que la composition contient entre 2% et

40% (p/p) de la première substance.

8. Une composition suivant l'une quelconque des revendications **1** à 7, caractérisée en ce que l'ingrédient actif comprend un médicament insoluble dans l'eau.

9. Une préparation pour une utilisation dans la production d'une composition pharmaceutique solide à libération contrôlée comprenant une matrice de la première substance choisie parmi un polydextrose soluble dans l'eau et un cyclodextrine soluble dans l'eau et une deuxième substance choisie parmi un alcool gras en C_{12} - C_{36}, de préférence en C_{14} - C_{22}.

10. Une préparation suivant la revendication 9, caractérisée en ce que la première substance comprend un cyclodextrine, de préférence un beta-cyclodextrine, et la deuxième substance comprend un alcool gras en C_{14}-C_{22},de préférence l'alcool stéarylique, l'alcool myristylique, l'alcool cétylique ou l'alcool cétostéarylique.

Patentansprüche

1. Festes Arzneimittel mit gesteuerter Freisetzung, umfassend einen in eine feste Matrix inkorporierten aktiven Bestandteil, wobei die Matrix eine erste Substanz, ausgewählt aus einer wasserlöslichen Polydextrose und einem wasserlöslichen Cyclodextrin, und eine zweite Substanz, ausgewählt aus einem C_{12}-C_{36}-Fettalkohol, vorzugsweise einem C_{14}-C_{22}-Fettalkohol, umfaßt.

2. Mittel nach Anspruch 1, dadurch gekennzeichnet, daß die erste Substanz ein Cyclodextrin, vorzugsweise ein beta-Cyclodextrin, umfaßt.

3. Mittel nach Anspruch 1 oder 2, dadurch gekennzeichnet, daß die zweite Substanz einen C_{14}-C_{22}-Fettalkohol, vorzugsweise Stearylalkohol, Myristylalkohol, Cetylalkohol oder Cetostearylalkohol,umfaßt.

4. Mittel nach einem der Ansprüche 1 bis 3, dadurch gekennzeichnet, daß es zusätzlich einen Celluloseether, vorzugsweise eine Hydroxyalkylcellulose oder eine Carboxycellulose, enthält.

5. Mittel nach einem der Ansprüche 1 bis 4, dadurch gekennzeichnet, daß das Verhältnis von Polydextrose/Cyclodextrin/Celluloseether zu Fettalkohol in dem Mittel zwischen 6 bis 1 und 1 bis 6, vorzugsweise zwischen 4 bis 1 und 1 bis 4, liegt.

6. Mittel nach einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, daß das Mittel zwischen 1% und 80% (Gew./Gew.), insbesondere zwischen 1% und 50% (Gew.(Gew.), der ersten Substanz enthält.

7. Mittel nach Anspruch 6, dadurch gekennzeichnet, daß das Mittel zwischen 2% und 40% (Gew./Gew.) der ersten Substanz enthält.

8. Mittel nach einem der Ansprüche 1 bis 7, dadurch gekennzeichnet, daß der aktive Bestandteil einenwasserunlöslichen Wirkstoff umfaßt.

9. Präparation zur Verwendung bei der Herstellung eines festen Arzneimittels mit gesteuerter Freisetzung, umfassend eine Matrix aus einer ersten Substanz, ausgewählt aus einer wasserlöslichen Polydextrose und einem wasserlöslichen Cyclodextrin, und eine zweite Substanz, ausgewählt aus einem C_{12}-C_{36}-Fettalkohol, vorzugsweise einem C_{14}-C_{22}-Fettalkohol.

10. Präparation nach Anspruch 9, dadurch gekennzeichnet, daß die erste Substanz ein Cyclodextrin, vorzugsweise ein beta-Cyclodextrin, umfaßt, und die zweite Substanz einen C_{14}-C_{22}-Fettalkohol, vorzugsweise Stearylalkohol, Myristylalkohol, Cetylalkohol oder Cetostearylalkohol, umfaßt.

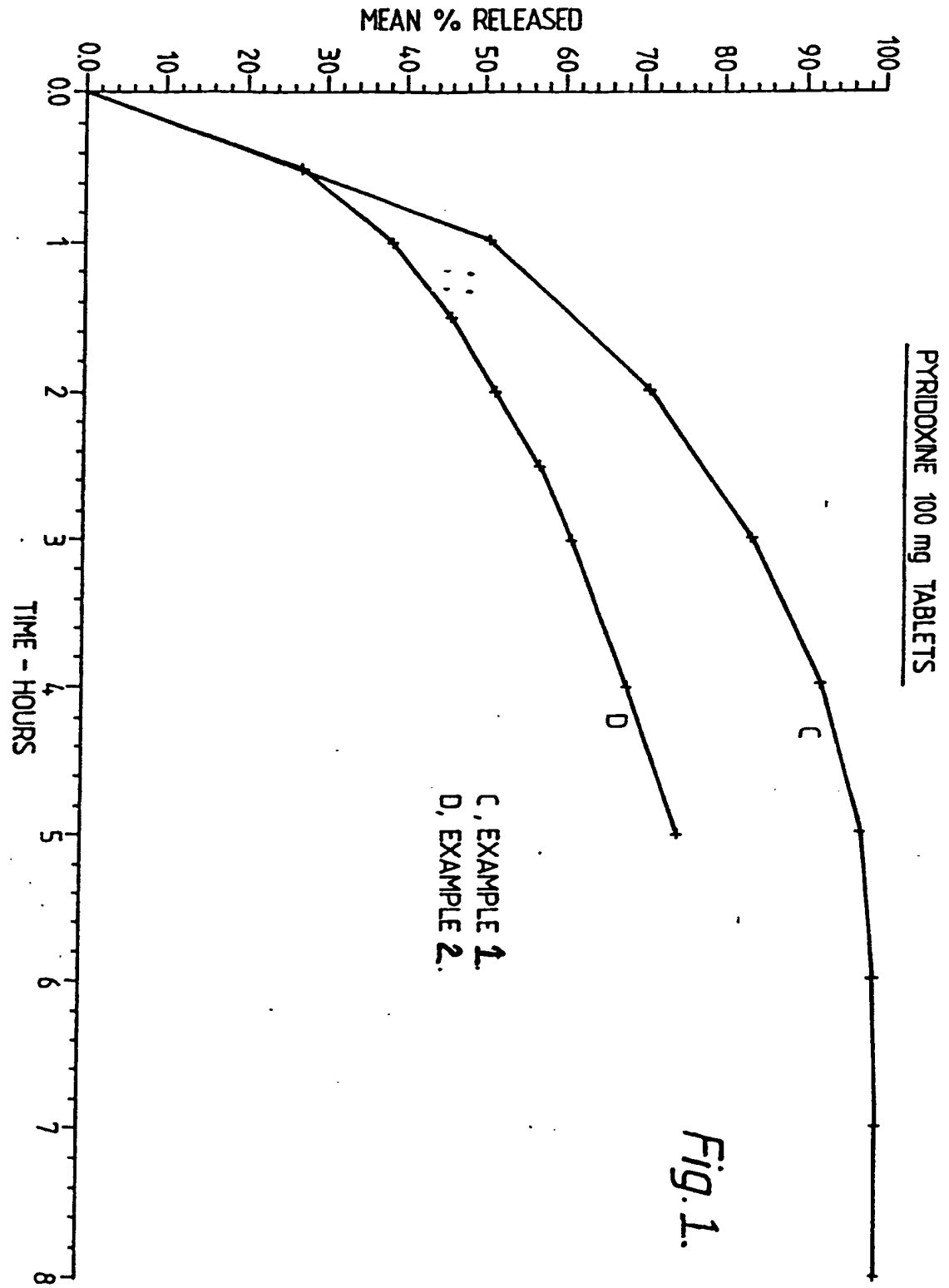
MEAN % RELEASED
0.0
10
20
30
40
50
60
70
80
90
100
TIME - HOURS
0.0
1
2
3
4
5
6
7
8
PYRIDOXINE 100 mg TABLETS
C
D
C, EXAMPLE 1.
D, EXAMPLE 2.

Fig. 1.

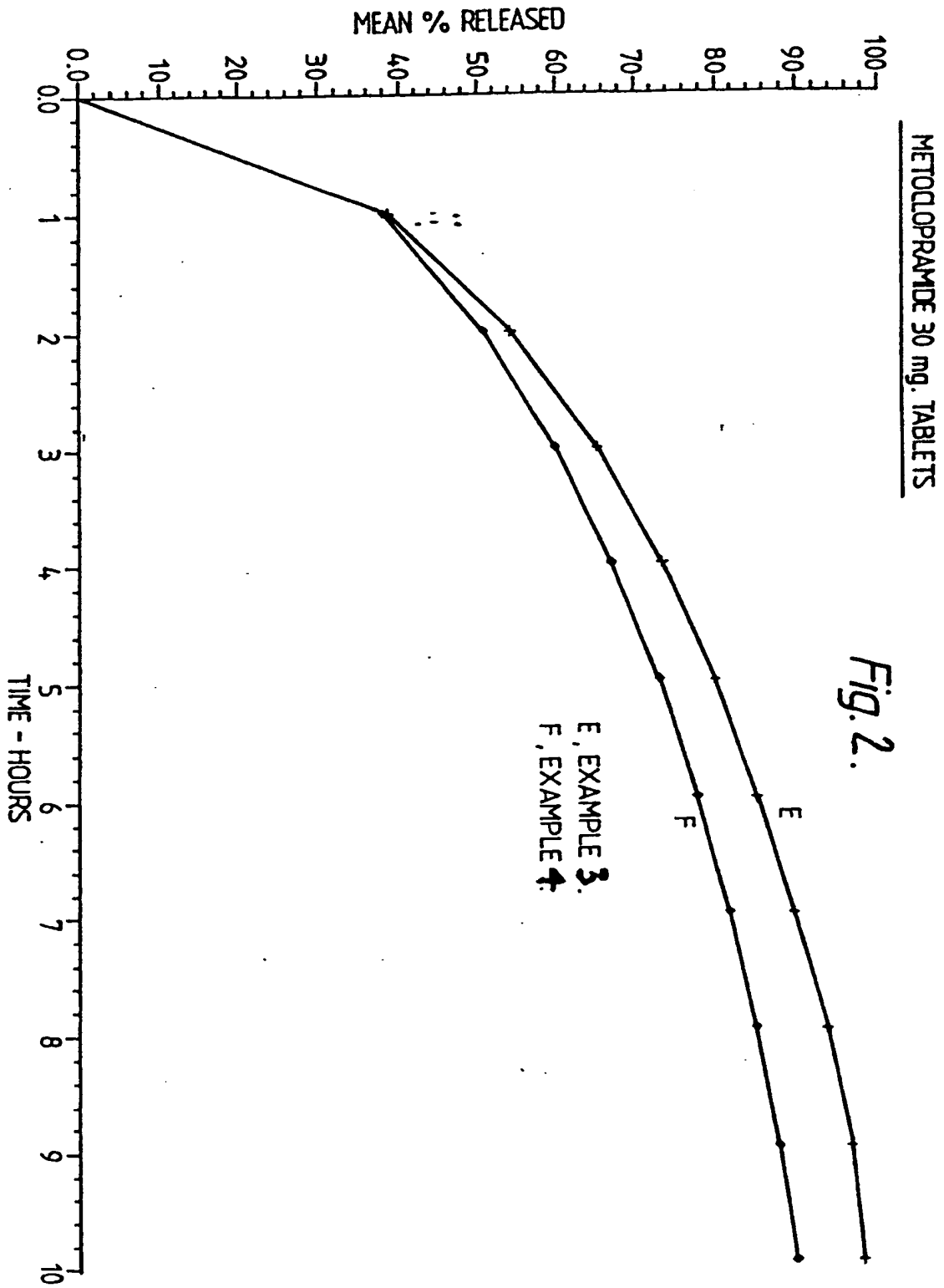
MEAN % RELEASED
0.0
10
20
30
40
50
60
70
80
90
100
TIME - HOURS
0.0
1
2
3
4
5
6
7
8
9
10
METOCLOPRAMIDE 30 mg. TABLETS
E, EXAMPLE 3.
F, EXAMPLE 4.
E
F

Fig. 2.